THE NATIONAL CHILDREN'S STUDY

THE NATIONAL CHILDREN'S STUDY
ENVIRONMENTAL MEASUREMENT ASSESSMENT

February 2013

Concept of Operations

Concept of Operations v2.0

Change History

Date	Version	Revisions	Author
1/17/2013	1.0		Drs. Michael Dellarco and Steven Hirschfeld
2/12/2013	2.0	Updated draft	Drs. Michael Dellarco and Steven Hirschfeld

Table of Contents

Executive Summary

The National Children's Study (NCS or the Study) is a national longitudinal study that will prospectively investigate the influence of biological, environmental, genetic, and social factors on the health and development of our nation's children. The NCS was mandated by the Children's Health Act of 2000 (Public Law 106-310) and is being implemented by the National Institutes of Health (NIH) with input from other federal government departments and agencies. The NCS is a data-driven, evidence-based, community and participant informed study.

The overall goal of the NCS is to collect information that will ultimately lead to improvements in the health, development, and well-being of children. The NCS design rests on the principle that both health and susceptibility to disease are determined by dynamic processes that can occur any time from preconception through adult life. In particular, the NCS will collect data geared toward broad outcomes of public health significance such as pregnancy outcomes, neurodevelopment and behavior, lung and airway disease, and physical growth and body maturation. Contacts with NCS participants will include in-person and remote visits during pregnancy, after delivery, and throughout infancy and childhood to collect biospecimens, environmental samples, physical measurements, examinations of child behavior and development, and information about the family.

The general principles that guide data acquisition and analysis for exposures of interest are:

- Definition of environment is broad
- Emphasis on early data acquisition
- Priority of selection of exposures to assess based on potential public health impact, scientific opportunity guided by feasibility, acceptability, cost
- Modality determined by data quality, stability, storage conditions, available analytic techniques guided by feasibility, acceptability, cost
- Modular design with core questionnaire, additional focused modules, analysis by missing by intent and imputation
- Longitudinal exposure data and area under the curve analysis
- Exemplar hypotheses to guide design and implementation logistics
- Integration of NCS exposure data with extant data sources

Purpose of This Document

The purpose of this document is to introduce the principles of environmental data acquisition and analysis in the National Children's Study. This document is aimed at a general audience with familiarity with the NCS and is not intended as a comprehensive, end-to-end overview of the environmental goals and practices of the NCS, nor, as a manual of operations. However, it will act as a foundation that will be augmented with

supplemental documentation containing greater detail. These additional materials are intended to remain as internal technical documents that will elaborate on specific operations such as modalities, quality, preparation, storage, instrument development, analytics, sample repositories, and other themes.

An Introduction to the NCS

The National Children's Study is a national longitudinal study that will prospectively investigate the influence of biological, environmental, genetic, and social factors on the health and development of our nation's children. The NCS was mandated by the Children's Health Act of 2000 (Public Law 106-310) and is being implemented by the National Institutes of Health (NIH) with input from other federal government departments and agencies. The NCS is a data-driven, evidence-based, community and participant informed study.

The overall goal of the NCS is to collect information that will ultimately lead to improvements in the health, development, and well-being of children. The NCS design rests on the principle that both health and susceptibility to disease are determined by dynamic processes that can occur any time from preconception through adult life. In particular, the NCS will collect data geared toward broad outcomes of public health significance such as pregnancy outcomes, neurodevelopment and behavior, lung and airway disease, and physical growth and body maturation. Contacts with NCS participants will include in-person and remote visits during pregnancy, after delivery, and throughout infancy and childhood to collect biospecimens, environmental samples, physical measurements, examinations of child behavior and development, and information about the family.

The NCS approach is to investigate the separate and combined effects of: environmental exposures (biological, chemical, physical, behavioral, economic, and psychosocial); gene-environment interactions on pregnancy outcomes; and precursors of adult disease of child health and development. Study visit measures will include, but are not limited to, language, culture, change in location, travel, access to health care, participation in organized activities, recreational opportunities, structured learning, out of home child care, and community involvement. Participants will be monitored to assess their exposure to food contaminants and supplements, medicinal products and devices, environmental chemicals and toxins, noise, and natural events prior to, and during, pregnancy.

Examples of exposures of potential interest to the NCS are:

- Natural products and industrial chemicals and byproducts in the air, water, soil, and commercial products
- Pharmaceuticals used for therapy and in the environment
- Radiation
- Proximity to manufacturing, transportation, and processing facilities
- Living with animals, insects, plants, media, and electronic device exposure

- Noise
- Access to routine and specialty health care
- Structured and unstructured learning opportunities
- Diet and exercise
- Family and social network dynamics in a cultural and geographic context

A non-exhaustive list of examples of outcomes of potential interest to the NCS includes:

- Premature birth
- Birth defects
- Growth and development
- Interpersonal relationships and bonding
- Inflammatory processes including allergies, asthma, and infections
- Epigenetic status
- Epilepsy and other neurologic disorders
- Cardiovascular function
- Cancer
- Multidisciplinary multidimensional aspects of sensory input
- Autism and other neurodevelopmental disorders
- Learning and behavior
- Precursors and early signs of chronic diseases such as obesity, asthma, hypertension, and diabetes

The NCS as a System

The NCS should be viewed as an integrated system comprised of many processes and components, not just a single study protocol. By framing the NCS as an integrated system, it is possible to better understand the relationships of its many components, thus identifying interdependencies and priorities which allows for effective resource allocation. A systems approach provides flexibility whereby activities can be reprioritized, reassigned, and reallocated in a dynamic fashion. The capacity to effect rapid changes provides benefits within the context of the larger system, even if a given operation may see a shift in resources and responsibilities. The flexibility of this approach also accommodates the funding environment of the NCS, permitting the proposal and evaluation of multiple scenarios to accomplish the Study goal. As an integrated system, the NCS has the opportunity to synthesize data coming from a variety of inputs simultaneously, thus enhancing its overall scientific contribution. This integrated system has several data acquisition strategies that highlight the scope and interdependencies of the NCS, including:

- **Vanguard Study:** A pilot study, which is an operational study aimed at understanding the feasibility, acceptability, and cost of recruitment, operations, logistics, and visit assessments to inform the Main Study
- **Main Study:** The Study activity that will focus on exposure-response relationships and be designed based on the data and evidence obtained from the Vanguard Study

- **Formative Research:** Defined limited-scope and limited-duration research projects that address technical or methodological questions required to responsibly and effectively design components of the Vanguard Study or Main Study
- **Substudies:** Studies that are embedded within the Vanguard Study and, in the future and when applicable, the Main Study, to address specific operational or scientific questions

The Vanguard Study is intended to remain dynamic in nature and content in order to evaluate multiple procedural and operational scenarios in terms of feasibility, acceptability, and cost.

The Environmental Domain

Broad Definition of Environment

The environmental domain provides information about participant exposure from environmental constituents, contaminants, behaviors, and psychosocial interactions. Information will be obtained about environmental exposures that can occur in the workplace, at home, in the community, during the commute to and from work, while exploring hobbies, and within individuals' lifestyles. Environmental Study visit measurement assessments will be conducted by several types of procedures including collection of biospecimens and environmental samples to assess environmental exposures, observations of the interior and exterior of residences and neighborhoods to identify environmental contaminant sources and neighborhood characteristics, and questionnaires administered to participants to learn about environmental exposures based on occupation, lifestyle, and daily routine. Additionally, interviews, questionnaires, and standard tests will be administered to assess family dynamics, the social behavior, and neurodevelopmental and physical growth landmarks of the child.

An array of environmental exposures may occur during intervals of child growth and development. A workshop convened by the NCS in 2011 further confirmed that during growth and development the fetus and young children may be refractory or susceptible to certain environmental contaminants. Detection of these contaminants may be difficult due to the lack of measurement methods or specificity of biological markers.

Emphasis on Early Data Acquisition

Due to the lack of knowledge about which environmental exposures are important and which growth and development intervals should be measured, especially those later in

life, the NCS intends to measure a wide array of environmental exposures at frequent intervals to capture as much information as possible, especially during the early stages of life. The merit of this approach is supported by recent reports that suggest an association between autism and maternal infections during pregnancy as well as, the finding of a causal role for de novo mutation for impaired brain function disorders such as schizophrenia, dyslexia, and reduced intelligence in children to a paternal age effect. While not the complete story, the NCS believes it would be short sighted to limit sample collection and analysis to those environmental exposures currently considered to be the cause of outcomes of interest. An evidence based approach aligns with the NCS system because methods can be modified to consider new scientific knowledge or investigate issues in greater detail with substudies when warranted by observed outcomes in the cohort.

Study Visit Approach

Collection of environmental exposure information is particularly challenging in the NCS cohort due to the goal to "perform complete assessments of environmental influences on children's well-being". There is a diverse array of environmental exposures that include biological, chemical, physical, socioeconomic, and social. Many exposures can be intermittent and of variable intensity. There is awareness that exposures during critical periods of child growth and development, including in utero and later in life, may be important. However, growth and development stages are not well defined. Exposures early in life may not influence the expression of adverse health outcomes or disease until later in life. In particular, efforts to collect environmental exposure information prior to pregnancy, during pregnancy, and at birth presents advantages, opportunities, and challenges (see Table 1). Additional environmental exposure information can be collected by enrolling women into the Study at preconception or early in pregnancy. However, doing so entails logistical costs to identify, recruit, and consent women into the Study and to schedule Study visits prior to, and during, their pregnancy. The NCS plans to enroll women at preconception, during pregnancy, and at birth in varying proportions to obtain information about environmental exposures prior to conception and during pregnancy.

Table 1. Advantages, opportunities, and considerations for environmental exposure information collection from different cohort phases.

Cohort Phase	Advantages	Considerations or Challenges
Preconception	Ability to collect preconception samples and document prenatal exposures prospectively increasing reliability of exposure assessment Ability to document time to pregnancy, infertility, and early fetal loss	Not all women consented will conceive and enter subsequent phases of the study Broad array of environmental study visit measurement assessments required to document environmental exposures Prospective environmental exposure study visits for a large number of women will be required
Prenatal Cohort	Ability to collect prenatal samples and document exposures prospectively Ability to document fetal loss	The timing of entry into the study can vary due to gestational age at consent Early pregnancy visits may be missed due to timing of entry into the study Preconception environmental exposures must be assessed retrospectively Differential cooperation and recruitment rates could introduce bias Variable demographics of women who seek prenatal care could introduce bias
Birth Cohort	Participants would be enrolled with approximately the same starting point High expected rate of enrollment of newborns Broad demographic profile because most births occur in hospitals or birthing centers Enhanced feasibility of collection of birth samples (cord blood and placental tissue) as participating hospitals will be known in advance facilitating establishment of operational aspects of the collection	Prenatal and preconception exposure information must be collected retrospectively Subsequent pregnancies of participants could be enrolled to capture prenatal or preconception exposure data, but this would miss data on first pregnancies and may be biased Differential cooperation and recruitment rates could introduce bias

Modular Design

The NCS will emphasize data collections early in pregnancy and early in child development because the largest knowledge gaps, and perhaps the most critical

events, occur during these time periods. Pregnancy data collections will be scheduled at least twice, if possible, prior to approximately 20 weeks gestation and once later in pregnancy. Data collections for children are scheduled at birth, and every 3 months for the first year, and every 6 months until 5 years old, for a total of 13 opportunities for data collection. Seven visits will be in-person, at the home or the clinic, and may include biospecimen and environmental data collection. The other six visits are remote collections, typically by telephone interview. Subsequent data collections have not been scheduled, but will be, on average, about every other year until 21 years old for a total of 8 additional data collection opportunities. In sum, 21 data collection opportunities, per child, are planned.

Table 2. Proposed Study visit schedule.

Birth	Place of Delivery
Prenatal visits	Home
3 months	Phone
6 months	Home
9 months	Phone
12 months	Clinic or Home
18 months	Phone
24 months	Clinic
30 months	Phone
36 months	Clinic or Home
42 months	Phone
48 months	Clinic
54 months	Phone
60 months	Clinic or Home

A core questionnaire will be administered at every childhood visit. In addition, supplemental modules will be administered based on events and conditions such as age, developmental stage, and other triggers such as specific exposures or hospitalizations. While the core questionnaire is intended for all participants, supplemental modules will be administered to a subset of the cohort on a missing, by design basis to leverage the large Study population and extend resources. The visit schedule is flexible, in that children will not have assessments administered precisely at a given age but, instead, within a window of several weeks around a particular age to improve compliance and to capture data across a range of specific ages. In addition to questionnaires, other modalities for data capture such as sounds, images, geographic movements, and mapping of social interactions and networks may be used. The core questionnaire and other questionnaires are essential to calibrate the data from other modalities and to link NCS data to other data sources. This module-based visit strategy is intended to collect information about specific exposures or observed outcomes, with consideration for development stages or exposure events, while decreasing the burden on respondents as all the modules will not be offered to all participants.

Environmental Exposure Data Acquisition

Under the current planned Study visit approach, biospecimens, blood, and urine are scheduled to be collected from the mother prenatally, at birth and when the child is 6 months and 12 months old. From ages 2 years to 5 years, blood and urine will be collected from the child. After birth, breast milk will be collected from the mother. At each of these opportunities, except birth, the mother will be asked to complete a questionnaire. During in home visits, structural observations of the interior and exterior of the dwelling will be conducted and house dust will be collected. Air contaminants trapped on filters, noise measurements, and tap water samples may be collected from some participants' homes during in home visits associated with administration of supplemental modules.

Exposure Priority Selection

Exposure information will be collected based on outcomes of interest with consideration for the public health importance of the outcome and scientific opportunity followed by availability of Study visit measurement assessments and sampling considerations such as invasiveness, sample matrix, and analyte stability; informative value and cost of sample collection; and options for administration of other Study visit measurement assessments to collect the same kind of information about an environmental exposure. Appendix A shows examples of environmental exposures of interest in the NCS including exposure to inorganic and organic chemical compounds, metals, microorganisms, and particulate matter. Sources of environmental exposure may include: industrial polymers and organic compounds found in adhesives, carpeting, insecticides, lubricants, package coatings, soil repellents, stains, specialty papers, pharmaceuticals, and textiles among others; contaminants and constituents found in drinking water including microorganisms and radioactive elements; dietary sources including microorganisms and dietary supplements; constituents of tobacco smoke; and combustion products from heating appliances. Examples of outcomes of interest include: fetal development, pre-mature birth and congenital defects (polycyclic aromatic hydrocarbon metabolites); interference with intermediary metabolism leading to malignancy, inflammation, cardiovascular disease, and diabetes (arsenicals); and disrupted lipid metabolism and weight regulation (polyfluroalkyl compounds). Study visit measures, primarily biospecimens, blood, and urine, provide opportunities for collecting information about many of these exposures. In those instances where a biospecimen cannot be collected, or does not provide informative value, environmental samples, observations, questionnaires, or extant data will be collected to provide information about environmental exposures.

Modality Determination

Use of Exemplar or Model Hypotheses

Since there is no universal and unambiguous definition of health, the NCS plans to employ investigation of a select number of prioritized model exposures and outcome hypotheses. Exposure outcome hypotheses will be prioritized with consideration for the public health importance of the outcome, availability of Study visit measurement assessments, and sampling considerations such as sample matrix, specificity and stability of analytes, informative value, and options for other Study visit measurement assessments to collect the same kind of information. Each exposure will be assigned to each outcome in a matrix table to generate model hypotheses as a reference point to test many other hypotheses, including those that may not be envisioned at this time. For example the appearance of a chronic inflammatory condition may result from an interaction between host characteristics that include genotype and exposures that may include diet, microbiome, and infection. Another example may be that exposure to nuts may have a beneficial effect in some people and may provoke a life threatening allergic response in others.

In our model hypothesis paradigm, selected exposures proposed as surrogates for additional exposures are:

Analysis of
- Heavy metals
- Pesticide residues
- Semi-volatile organic compounds
- High frequency sound

In samples of
- Household dust
- Blood
- Urine
- Questionnaires on exposures including social environment

The select outcomes proposed as surrogate outcomes for additional outcomes are:
- Linear growth rate and body mass index as a surrogate for general health
- Metabolic screen of serum total protein, blood urea nitrogen, cholesterol, iron, and calcium for nutrition and dietary exposure
- Frequency and duration of health system encounters for respiratory illness for pulmonary health
- Timing of standard neurodevelopmental landmarks and any deviation from adjusted trajectory for cognitive and social development

Using this approach, a model hypothesis for testing a design could be pesticide residues in household dust as the exposure and linear growth rate and body mass index as the outcome.

Table 3. Exemplar exposure outcome matrix.

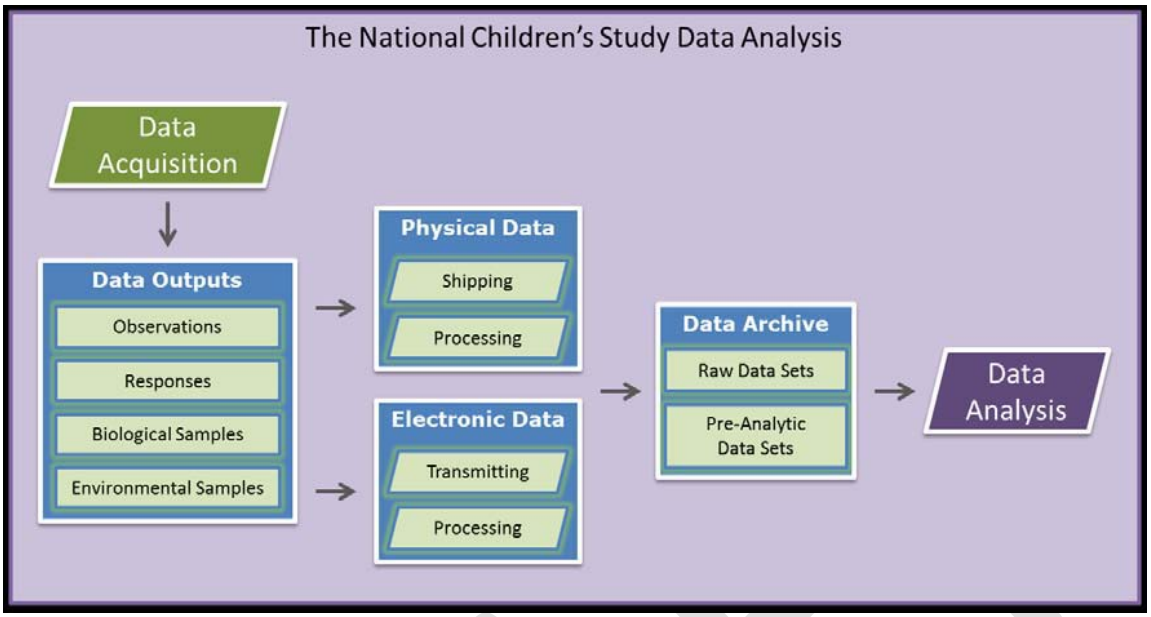
Exemplar Outcomes	Exemplar Exposures				
		Heavy metals	**Pesticide residues**	**Semi-volatile organic compounds**	**High frequency sound**
	Linear growth rate and body mass index	*Correlation Estimate*	*Correlation Estimate*	*Correlation Estimate*	*Correlation Estimate*
	Serum metabolic screen	*Correlation Estimate*	*Correlation Estimate*	*Correlation Estimate*	*Correlation Estimate*
	Frequency and duration of respiratory illness	*Correlation Estimate*	*Correlation Estimate*	*Correlation Estimate*	*Correlation Estimate*
	Neurodevelopmental landmarks	*Correlation Estimate*	*Correlation Estimate*	*Correlation Estimate*	*Correlation Estimate*

Data Analysis

The analysis of data in the NCS is driven by an understanding of the types of data available, the format of the data, and the organization and location of the data. Data acquired from participants and their environments is quality checked and archived, and then able to be processed and analyzed. Data, in the form of biospecimens or environmental samples, is considered latent data in that the specimen or sample must be processed and then generally assayed before statistically analyzable data emerges. As shown in the work process flow diagram (Figure 1), all data can follow one of several pathways:

- **Immediate analysis at the time of collection:** Examples are physical measures that can be readily entered into a database that has parameters for accepting only plausible values or a biofluid that is analyzed at the time of collection using point of care technology.
- **Data acquisition and subsequent transfer of the data to be processed at another location and time:** Examples are biospecimens, such as fluids, that are shipped to a clinical laboratory for processing and analysis or data from a cognitive assessment instrument that are processed for quality control and calculation of an integrated or composite score.
- **Data acquisition and subsequent transfer to an archive, either digital or physical, for subsequent processing and analysis:** Examples are environmental samples that are shipped and stored or responses to questions that are transferred to a digital archive.

Figure 1. Overview of data analysis in the National Children's Study.



All pathways eventually lead to analysis and production of analytic data sets. No matter which pathway the data follow, the individual data elements will be tagged and catalogued on the basis of numerous codes, allowing the NCS to track the life cycle of each data point. Some types of codes attached to data are: participant code (a code generated without any personally identifiable information (PII), date and time stamp of data collection for an instrument or sample collection procedure, Study site code, sample processing or shipping data, and relationship to other data elements. Collectively, all the information for the data elements, whether digital or physical, will be available in a catalog.

Data Repository

The Vanguard Data Repository (VDR) is a family of databases joined in a workflow. The data are submitted without PII linked to the exposure and response data elements based on a list of pre-identified data fields. Although the PII fields are collected, they are retained elsewhere in the system and not transmitted to the central VDR.

Sample and Specimen Repository

The NCS Repository receives, processes, and stores biological and environmental samples for later analysis when needed. There is an exception for those environmental samples that are collected for analytes which are labile and must be analyzed within a

specific time window. These samples are shipped to a contract analytical laboratory where they are processed and analyzed upon receipt.

Archiving tasks are highly technical and require extensive experience, expertise, specialized facilities, and long-term commitment. Each Study participant's samples are unique and cannot be replaced if lost, damaged, or contaminated. Therefore, it is essential that samples are stored under optimal conditions which necessitate a wide range of storage temperatures, avoiding the potential of cross-contamination with respect to environmental contaminants or degradation, and avoiding loss of, or damage to, samples due to a natural or manmade disaster. Analyses are routinely conducted to ensure sample collection containers and processing equipment is free from chemical contaminants or interfering chemical compounds. Stability studies are currently being conducted to ensure that the conditions and procedures for storing biospecimens, environmental samples, and their extracts preserve the integrity of the sample for analysis in the future. Studies are being conducted with dust samples and pesticide residues to determine the effect of storage conditions on sample quality and analyte integrity. Results will inform processing and storage procedures used in the NCS and ensure samples are preserved for later use.

The NCS continues to explore options in building capacity to continually process, store, and retrieve samples and data in a form suitable for future scientific research that is simple, reliable, cost-effective, and pragmatic for both the NCS research community and future researchers. Investment in automated robotic processing equipment has been made to improve efficiency and reduce the cost of biospecimen processing. Investigation of innovative storage procedures, such as gel polymer encapsulation of biological fluids and specimens, is being conducted to determine if biological specimens can be encapsulated and stored at room temperature without loss of specimen quality and analyte integrity.

Data Processing

Once environmental samples have been processed and analyzed, digital analytic data sets will be sent to the VDR and archived. Analytical laboratory data reports from analysis of biospecimens and environmental samples for chemical contaminants will be submitted to the NCS Environmental Domain contractor for review to ensure samples were processed properly and analyzed according to method specifications with proper quality control performance. Analytic data sets will be cataloged on the basis of domains and content.

Environmental sample collection and analysis procedures capture metadata, defined as data about the data. This includes information such as which Study visit, when and where the sample was collected, and by whom. Data tagging is an impotent aspect of metadata development to be able to investigate Study visit characteristics and relationships that may be informative about observed outcomes. Because data tagging for environmental measures is not well defined, the NCS is developing data tagging in consultation with partners such as the National Cancer Institute (NCI),

Centers for Disease Control and Prevention (CDC), and other large scale birth cohort study investigators.

Environmental Study Visit Measure Evaluation

Environmental Study visit measurement assessments are evaluated in the Vanguard Study for feasibly, acceptability, and cost. Feasibility is based on the technical performance of Study procedures and operations. Acceptability is assessed in terms of the impact of Study procedures and operations on participants and infrastructure. Cost is ascertained through qualitative and quantitative assessments of the level of effort, material, logistics, and funds required to implement the Study procedures and operations. Additionally, environmental Study visit measures are evaluated in terms of scalability, the ability to be deployed efficiently across the cohort at the desired time intervals of interest, and the ability to provide informative value about environmental exposures.

Experience in the initial Vanguard Study showed that participants accepted the Study visit measurement assessments deployed, but many of the environmental sample collection and analysis procedures were not feasible due to the amount of equipment involved, the logistics associated with setup and retrieval, and the cost incurred with sample collection and analysis. This finding necessitated an evaluation of environmental Study visit measures, investigation of participant sample collection in the Vanguard Study, formative research, and partnership collaboration to improve environmental Study visit measures for the Main Study.

Longitudinal Exposure Data Analysis

Data analysis will examine the longitudinal aspect of individual exposures with a goal to generate distributions and area under the Curve calculations when appropriate. Absent longitudinal data for a particular exposure, point estimates, and comparison to participants and environments with similar characteristics may still allow calibration.

The NCS data systems are designed to be as interoperable as feasible to leverage extant data sources. When feasible and justified, exposure data may be obtained using either solely extant sources or a blend of collected data plus extant sources. For example, outdoor air quality may be inferred from models of historic data that cover a period of interest.

Formative Research

Environmental formative research studies are short term methodological studies designed to evaluate or modify methods to improve the performance, or efficiency, or to document performance to provide assurance that the measurement methodology

will meet the needs of the NCS Main Study. NCS environmental formative research is being conducted to determine and document the stability of stored environmental samples, extracts, and analytes; improving the informative value of dwelling unit observation instruments and questionnaires; and the development of near real time sensor based environmental measurement devices for multiple air pollutants. Results of formative research projects will be evaluated and compared to the performance and results of environmental Study visit measures in the Vanguard Study to develop scalable Study visit measures optimized for economy, efficiency, and informative value for the NCS Main Study.

Partnerships and Use of Extant Data Sources

The NCS partners with other NIH institutes, federal government agencies, and other institutions and organizations to utilize the experience and expertise of subject matter experts in specific domains to address specific issues of interest. In the Environmental Domain, collaborations and partnerships are underway, or planned, to address environmental sample collection, analytical methodology for chemical residue detection, questionnaire development and validation, and participant mobility monitoring. Table 4 shows a list of NCS partners investigating environmental measurement methodology including CDC's National Center for Environmental Health; US Environmental Protection Agency's (EPA's) Office of Pesticide Programs; Heath Canada for analysis of biospecimens for environmental chemical residues; *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD); National Institute of Environmental Health Sciences (NIEHS), with the United States Geological Survey (USGS), for geographic information system platform development and data mapping; National Cancer Institute (NCI) for development and deployment of dietary surveys; NCI and the Environmental Health Risk in European Birth Cohorts (ENRICO) for the evaluation, validation, and assessment of the informative value of environmental health questionnaires; Los Alamos and Sandia National Laboratories for development and evaluation of encapsulation technologies to store biospecimens at room temperature; and Ginger.io and Google for development of participant experience mobile monitoring methodology.

Table 4. Examples of current and historic partnerships for environmental exposure methods development in the National Children's Study.

Organization	Topic Area
ENRICO	Environmental exposure question validation
EPA	Breast milk analytical method for pesticides
Health Canada	Environmental contaminants in biospecimens
NICHD, NIEHS	GIS mapping techniques
USGS	Water quality measurement methods
Google	App development for behavior monitoring
Ginger.io	Participant mobility monitoring
Research Triangle Institute	Personal air monitors

Additionally, The NCS actively interacts with investigators developing new technologies that have the potential to improve efficiency, economy, and informative value of environmental Study visit measures. Specifically, the NCS is investigating the feasibility of near real time air and water monitoring devices that can record the presence of contaminants at Study locations quickly; analytical methods that can detect a broad array of chemical contaminants in microarray assays using blood or saliva; exploring environmental exposures through systems biology analysis of biological networks; and mobile monitoring methodology and crowd sourcing techniques.

Harmonization

Data sharing and integrated analyses rely on harmonized concepts, comparable methodology, shared terminology, and accessible data fields. Harmonized terminology is a fundamental step toward enabling interoperability. Consistent terminology bridges concepts among multiple disciplines across developmental stages to improve data sharing and data integration. Efforts to understand child growth and development are further complicated by the lack of consistency in terminology and assessment methodology.

The NCS participates in the NICHD Pediatric Terminology Harmonization Initiative to develop and apply harmonized pediatric concepts, and their corresponding data elements, based on a developmental stage framework that follows a child's growth and development through the various life stages from pre-birth to 21 years of age. (See: http://www.nichd.nih.gov/health/clinicalresearch/clinical-researchers/terminology).

Deployment of environmental exposure Study visit measurement assessments are aligned with the child growth and development stages described in this initiative.

NCS environmental exposure Study visit measurement assessments employ glossary terminology in protocols, standard operating procedures, laboratory analysis methods, and data transmission and analysis operations. The NCS maintains a glossary for Study visit terminology to define terms such as instrument, method, procedure, and sample which may have a different meaning among disciplines. The glossary serves as an essential tool for communication among NCS Program Office staff, support contractors, and subject matter experts, in development of Study visit measurement methods and data evaluation in protocol development, assignment of measures to Study visits, and data analytics.

The NCS participates in birth cohort working groups to share information and harmonize Study visit measurement procedures to enable comparison of Study design and data collection procedures, Study visit measurement results, and sharing of data to expand investigation of exposure outcome relationships. The Environment and Child Health International Birth Cohort Group, comprised of birth cohort studies being conducted in China, Japan, France, Germany, and the NCS, harmonizes Study visit schedules, measurement methodology and procedures, logistics, and data analytics to harmonize the process and approach for sample collection and analysis that permits comparison of results and data sharing to expand investigation of outcomes of interest. The International Childhood Cancer Cohort Consortium (I4C) aims to examine associations between environmental exposures and the incidence of childhood cancers by pooling prospective population data from one million pregnant mothers and their babies. The NCS is engaged in data pooling exercises for specific Study visit measures dealing with birth outcomes and pesticide exposures to determine the influence, if any, on the development of cancer in children.

The benefits of harmonization are the development of standard pediatric terminology for child growth and development research, optimization of Study visit measurement procedures to investigate exposures of interest, opportunities to compare results of exposure outcomes of interest, and development of a learning community to expand investigations to improve the health of children everywhere.

Selected Bibliography

Brent RL, S Tanski and M Weitzman (2004) A Pediatric Perspective on the Unique Vulnerability and Resilience of the Embryo and the Child to Environmental Toxicants: The Importance of Rigorous Research Concerning Age and Agent, Pediatrics 113, 935-944.

Brown AS (2012) Epidemiologic studies of exposure to prenatal infection and risk of schizophrenia and autism, Devel Neurobio, 72, 1272-1276

Hines RN, D Sargent, H Autrup, LS Birnbaum, et al (2010) Approaches for Assessing Risks to Sensitive Populations: Lessons Learned from Evaluating Risks in the Pediatric Population, Tox Sci 113, 4–26

Kong A, ML Frigge, G Masson, S Besenbacher, et al (2012) Rate of de novo mutations and the importance of father's age to disease risk, Nature 488, 471-475.

Appendix A - Potential Environmental Exposures of Interest

Exposures	Exposure Sources	Examples of Specific Analytes	Potential Examples of Outcomes of Interest	Considerations	Proposed Study Visit Measure	NCS Proposed Approach	Other Potential Options to Evaluate				
General (All Participants)							Biomarker	Environmental Sample	Extant Data	Questionnaire	Direct observation
Nicotine and hydrocarbons	Tobacco smoke	Cotinine	Addiction, neurochemical changes, malignancy, respiratory effects, lung function decrements	Limited to ~ prior 72 hours exposure, better quantification in serum, higher concentrations in urine, questionnaires generally unreliable, serum collection generally feasible in children 24 months or older	Questionnaire plus Blood (serum)	Biomarker	Urine	Air - particulate matter	Gallup Poll - Smoking in the USA	Smoking history	Smoking materials in home
Polyfluoroalkyl Compounds	Industrial polymers found in textiles and carpets; consumer products including adhesives, lubricants, package coatings, stains, soil repellents, insecticides, specialty papers, and pharmaceuticals	2-(N-Ethyl-perfluorooctane sulfonamido) acetic acid (Et-PFOSA-AcOH), 2-(N-Methyl-perfluorooctane sulfonamido) acetic acid (Me-PFOSA-AcOH), Perfluorodecanoic acid (PFDeA), Perfluorohexane sulfonic acid (PFHxS), Perfluorononanoic acid (PFNA), Perfluorooctanoic acid (PFOA), Perfluorooctane sulfonic acid (PFOS), Perfluorooctane sulfonamide (PFOSA)	Disrupted lipid metabolism and weight regulation	Limited to exposures less than 3-4 days prior to sampling	Urine	Biomarker	Blood (serum)	Dust	Whole Foods Survey consumer packaging preferences	Carpet, furniture, clothing stain repellants	New carpeting and furniture, food storage containers
Metals	contaminants in drinking water and dietary sources	Barium, Beryllium, Cadmium, Cobalt, Cesium, Manganese, Mercury, Molybdenum, Lead, Platinum, Antimony, Selenium, Tin, Thallium, Tungsten, Uranium	Cadmium - bone and kidney effects, lead and mercury-neurological deficits, manganese - CNS effects, selenium - immune regulation	Long half life in weeks to months, could be assessed in bone and soft tissue	urine	Biomarker	Blood (serum)	Tap water	Water supplier monitoring reports, state household water satisfaction surveys	Source of drinking water	Age, condition, discoloration of water pipes and taps
Arsenic (speciated)	drinking water and dietary sources of exposure	Arsenobetaine, Aresenocholine, trimethylarsine, Monomethylarsonic acid, Dimethylarsinic acid, Arsenous (III) acid, Aresenic (V) acid	Interference with intermediary metabolism leading to malignancy, inflammation, cardiovascular disease; diabetes;	Limited to exposures less than 30 hours prior to sampling	urine	Biomarker	Blood (serum)	tap water	Water supplier monitoring reports, state household water satisfaction surveys	source of drinking water	age, condition, discoloration of water pipes and taps
Dialkyl phosphate metabolites of organophosphorus pesticides and Pyrethroid insecticide metabolites	Pesticide residues from diet	Standard organophosphate Screening Method	Neurological effects	Limited to exposures less than a few hours for non-fat soluble and a few days for fat soluble	Urine	Biomarker	Blood (serum)	dust	pesticide use surveys, product sale data	diet survey, pesticide applications	pesticide products
Phthalate metabolites	Chemical emissions from fixtures and furnishings	MCPP (MONO[CARBOXYNONYL]), MMP (MONO-METHYL), MCHP (MONO-CYCLOHEXYL), MOP (MONO-N-OCTYL) + others	Reproductive and endocrine effects	Limited to exposures less than 24 hours prior to sampling	Urine	Biomarker	Blood (serum)	Dust, surface wipes	Whole Foods Survey consumer packaging preferences	Medical device use	plastic food containers and toys, medical devices
Polycyclic aromatic hydrocarbon metabolites (PAHs)	Combustion products from smoking, particulate matter sources, and dietary sources	1-naphthol (1-NAP), 2-naphthol (2-NAP), 3-hydroxyfluorene (3-FLU), 9-hydroxyfluorene (9-FLU), 1-hydroxyphenanthrene (1-PHE), 2-hydroxyphenanthrene (2-PHE), 3-hydroxyphenanthrene (3-PHE), 1-hydroxypyrene (1-PYR), 2-hydroxyfluorene (2-FLU)	Fetal development, pre-mature birth, congenital defects	Limited to exposures less than7 days prior to sampling	Urine	Biomarker	Blood (serum)	Air - particulate matter	American Housing Survey	Smoking, heating appliances	Smoking materials in home, fireplace, woodstove

Exposures	Exposure Sources	Examples of Specific Analytes	Potential Examples of Outcomes of Interest	Considerations	Proposed Study Visit Measure	NCS Proposed Approach	Other Potential Options to Evaluate				
Phytoestrogens and metabolites	Ingested plant material	Isoflavonoids, the lignans or the coumestans.		Limited to exposures less than 1 day prior to sampling	Urine	Biomarker	Blood (serum)		Survey of estrogen therapies, medical supplement use	Diet survey, pharmaceutical use, medical supplement use, baby formula	Baby formula
Phenols	Chemicals in consumer products	2,4-Dichlorophenol (24 DCP), 2,5-dichlorophenol (25 DCP), Butyl paraben (B-PB), Methyl paraben (M-PB). n-Propyl paraben (P-PB), Benzophenone-3 (2-Hydroxy-4-methoxybenzophenone) (BP3), Bisphenol A (2,2-bis[4-Hydroxyphenyl] propane) (BPA), Triclosan (2,4,4'-Trichloro-2'-hydroxyphenyl ether) (TCS)	Endocrine disruption, epigenetic modification, cytokine release, and oxidative stress. reproductive disorders and increased risk of breast, prostate or testicular cancer in offspring	Limited to exposures less than a few (5-14) hours prior to sampling	Urine	Biomarker	Blood (serum)	surface wipe	Consumer product surveys	Consumer product use	Consumer product inventory
Phenols	Chemical residue in consumer products	Bisphenol A, (2,2-bis[4-Hydroxyphenyl] propane)	Reproductive effects, endocrine effects	Higher concentrations in breast milk than serum or urine, limited to exposures less than a few hours	Breast milk	Biomarker	Blood (serum)	Dust	Consumer product surveys	Use of plastic ware containers and products	Plastic water and food containers and toys
Organochlorines	Pesticide residues from diet	Organochlorines	Neurological effects, reproductive effects	Strongly lipid soluble, can sequester in body tissues with high lipid content for days - months	breast milk	Biomarker	Blood (serum)	dust	pesticide use surveys, product sale data	diet survey, pesticide applications, pet care	pesticide products, pets
Polyhalogenated compounds	Chemical residue in building materials, furnishings, and consumer products	PBDEs/PCBs	Endocrine disruption, neurological effects	Strongly lipid soluble, can bio accumulate, half life of several weeks for PBDE, months for PCBs	breast milk	Biomarker	Blood (serum)	dust	Housing characteristics surveys	new or recent household furnishings	new household furnishings
Pesticide residues, metals, semi-volatile organic compounds, polyhalogenated organic compounds	Diet may be a source of exposure to chemical contaminates	Cadmium, mercury, PBDEs/PCBs,	Endocrine disruption, epigenetic modification, cytokine release, reproductive disorders, neurological disorders, and malignancies	broad variable half life spanning hours-days	diet survey	Participant responses	Blood or urine	Food samples	Market basket surveys	Diet survey	Duplicate diet survey, videography
Noise	Noise outside and inside the dwelling	Traffic, construction	Sensory loss, stress, irritability	Variable duration and intensity depending on source	Questionnaire, inverviewer impression and spot sound pressure	Participant response, inverviewer impression and direct measure		Noise measurement	Community noise surveys	Noise questionnaire	Community observation of noise emitting sources
Volatile organic compounds, semi-volatile organic compounds	Emissions from fixtures, furnishings and consumer products, cleaners	Toluene, xylene, carbonyls (aldehydes, ketones)	Respiratory effects, cancer	Limited half-life in air of a few hours	Questionnaire	Participant responses		Air trap samplers	Consumer product surveys	Consumer product use	Inventory of consumer products
Selective (not all participants)											
Particulate matter (PM), Nitrogen dioxide	Smokers in the home, gas appliances, wood burning stove, fireplace	PM 2.5, NO_2	Respiratory effects	Resource intensive and requires cooperation of participant family	Air sample	Air trap samplers	Blood for PM	Air trap samples, surface wipes, dust	American Housing Survey	Smoking history, appliance use	Smoking materials in home, fireplace, woodstove
Disinfection by products, pesticides, pharmaceuticals	Contaminants in personal wells or public water supply source	Trihalomethanes, Haloacetic Acids	Low birth weight, preterm delivery, birth defects, reproductive effects	NCS staff trained to collect sample properly	Drinking water sample	Drinking water sample collection	Blood, urine	Drinking water sample	Water supplier monitoring reports, state household water satisfaction surveys	Source of drinking water	Age, condition, discoloration of water pipes and taps
Noise	Noise outside and inside the dwelling	Traffic, construction	Sensory loss, stress, irritability	Variable duration and intensity depending on source	Sound recording with frequency analysis	Direct measure	Hearing acuity test	Noise measurement	Community noise surveys	Noise questionnaire	Community observation of noise emitting sources